REMARKS

Applicants thank the Examiner for her careful consideration of the present application and of cited references 36-94 during the examination of this application. Applicants acknowledge with appreciation the withdrawal of the previous rejections over the prior art.

The amendments to the specification at page 55, line 20 find support in the specification, for example, at page 7, line 12 and from the incorporated reference Chari et al., U.S. Patent No. 5,208,020 (for example at column 7, lines 55-67 and column 8, lines 1-14, which teaches that a linker may be linked to a maytansinoid compound via a group SSR_1, wherein R_1 represents methyl, linear alkyl, branched alkyl, cyclic alkyl, simple or substituted aryl or heterocyclic). Applicants note that all references, such as U.S. Patent No. 5,208,020, were incorporated by reference into the specification as originally filed, as stated at page 77, lines 1-2.

The amendment to Claim 1 finds support in the specification, for example, page 21, lines 19-31, page 22, lines 19-20, at page 25, line 14, and elsewhere in the specification.

The amendment to claim 4 finds support in the specification, for example, at page 21, lines 19-22 and elsewhere in the specification.

The amendment to Claim 5 finds support in the specification, for example, at page 21, lines 30-31 and elsewhere in the specification.

The amendment to Claim 6 finds support in the specification, for example, at page 22, lines 19-20 and elsewhere in the specification.

The amendments to Claims 14 and 15 find support in the specification, for example, at page 6, line 17 and at page 22, lines 16-17 and 19-20.

The amendment to Claim 26 finds support in the specification, for example, at page 7, line 12, at page 55, lines 18-20, and elsewhere in the specification as originally filed.

The amendment to Claim 28 find support in the specification as filed, for example, at page 55, line 27.

The amendment to Claim 31 finds support in the specification as filed, for example, at page 7, line 12, in the specification at page 55, lines 18-20 as originally filed and as amended above, and in U.S. Patent No. 5,208,020, to Chari et al., which was incorporated by reference into the specification as originally filed (incorporation by reference at page 77, lines 1-2).

No new matter is added by way of the amendments.

Claims 1, 2, 4-6, and 8-48 are pending in the application. Claim 26 stands rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time of the invention, had possession of the invention. Claims 1, 4-6, and 8-48 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari et al.(U.S. Patent No. 6,436,931; hereafter "Chari") in view of Hudziak et al. (U.S. Patent No. 5,725,856, hereafter "Hudziak") and further in view of Lewis et al. (Cancer Immunol. Immunotherap. 37:255-263, 1993; hereafter "Lewis"). Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari (U.S. Patent No. 6,436,931) in view of Carter et al. (U.S. Patent No. 6,054,297; hereafter "Carter") and further in view of Lewis. Claims 1, 2, 4-6, 8-12, 14, 20-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari in view of Bacus et al. (U.S. Patent No. 5,514,554, hereafter "Bacus") and further in view of Lewis. Claims 1, 2, 8-14, and 20-33 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Huston et al. (U.S. Patent No. 5,877,305, hereafter "Huston") and further in view of Lewis. Claims 1, 2, 8-12, 22-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of King et al. (U.S. Patent No. 5,747,261, hereafter "King") and further in view of Lewis. Claims 1, 34, 44 and 45 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in combination with Hudziak, Bacus, Huston, or King in view of Lewis as applied to Claim 1 and further in view of Senger et

al. (U.S. Patent No. 6,022,541, hereafter "Senger"). Claims 1, 34-37, 42 and 43 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in combination with Hudziak, Bacus, Huston, or King in view of Lewis as applied to Claim 1 and further in view of Sliwkowski et al. (J. Biol. Chem. 269:14661-14665, 1994; hereafter "Sliwkowski") or Carter. Claims 1, 4-6, 8-19, 22-25, 27 and 32 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Iwassa (U.S. Patent No. 5,217,713, hereafter "Iwassa") in combination with Carter, Hudziak, Bacus, Huston, or King in view of Lewis.

Applicants respectfully traverse the above rejections, as discussed in the following remarks.

The Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 26 has been amended for clarity. As amended, Claim 26 recites that "R" may be SH or SSR_1, wherein R_1 represents methyl, linear alkyl, branched alkyl, cyclic alkyl, simple or substituted aryl or heterocyclic.

Claim 26 stands rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time of the invention, had possession of the invention. With regard to Claim 26, the Examiner stated that "the full scope of DM1 molecules is not adequately described, because the "R" group is not described " (page 17, paragraph 15, lines 5-6 of the paragraph).

Applicants respectfully submit that the specification as originally filed, including U.S. Patents that were incorporated by reference, provided support and examples to describe the "R" group to the full scope of the claims. Applicants thus submit that the full scope of DM1 molecules is indeed described so that one of ordinary skill in the art would know how to practice the invention. For example, Applicants draw the Examiner's attention to the specification at page 55, lines 15-20, in which it is disclosed that disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, and esterase labile groups are all suitable for linking DM1 to an antibody. In addition, the specification cites, for example, U.S. Patent No. 5,208,020, EP

Patent 0 425 235 B1, and Chari *et al. Cancer Research* 52: 127-131 (1992); these references are incorporated by reference (page 77, lines 1-2). Further examples are provided at page 55, lines 25-31 to page 56, lines 1-5. Applicants note that U.S. Patent No. 5,208,020 states that a linker may be linked to a maytansinoid compound via a group SSR_1, wherein R_1 represents methyl, linear alkyl, branched alkyl, cyclic alkyl, simple or substituted aryl or heterocyclic (Chari et al., U.S. Patent No. 5,208,020, column 7, lines 55-67, column 8, lines 1-14).

Accordingly, Claim 26 describing the "R" group, Applicants believe that the rejection to Claim 26 under 35 U.S.C. § 112, first paragraph, is overcome.

The Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1, 4-6, and 8-48 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 1 stands rejected, the phrase "the tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody" being said by the Examiner to be indefinite. Claims 4-6 and 14 stand rejected, the Examiner objecting to the terms "growth inhibitory," "induces cell death," and "induces apoptosis" for not reciting a specific cell line in which growth is inhibited, cell death is induced, or apoptosis is induced. Claims 14-15 stand rejected as allegedly being indefinite for lack of recitation of the appropriate ATCC number. Applicants respectfully traverse these rejections.

Claim 1 has been amended to more clearly state and to more distinctly claim an embodiment of the present invention. As amended, Claim 1 explicitly states that the determination that a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody is performed in a recognized *in vitro* model, animal model, or human clinical trial. In addition, in conjunction with the amendments to dependent Claims 4-6 and 14 reciting specific cell lines, one of ordinary skill in the art would know how to practice the claimed methods without undue experimentation. Accordingly, Claim 1 is not believed to be indefinite.

Claims 4-6 and 14 have been amended for clarity to explicitly name cell lines to be used in the claimed methods. Accordingly, Applicants believe that the Examiner's objections to the terms "growth inhibitory," "induces cell death," and "induces apoptosis" for not reciting a specific cell line in which growth is inhibited, cell death is induced, or apoptosis is induced are overcome and that Claims 4-6 and 14 are not indefinite.

Claims 14-15 have been amended to explicitly state the ATCC number relating to the antibody named in the original claim. As amended, Claims 14 and 15 state the name and the ATCC number; accordingly, Applicants believe that the claims are not indefinite and that the rejections under 35 US.C. §112, second paragraph, are overcome.

The Rejections to Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 33-41 under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Hudziak and further in view of Lewis.

Chari is presented by the Examiner as providing maytansinoid compounds (including maytansinol, maytansine, and maytansinol esters including DM1) attached to monoclonal antibodies or their fragments, and as providing methods of killing selected cell populations. Hudziak is presented by the Examiner to provide anti-ErbB2 antibodies and fragments, including growth inhibitory and cytotoxic ant-ErbB2 antibodies. Lewis is presented by the Examiner as discussing tumor cells that overexpress ErbB2 and fail to respond to murine antibody 4D5 by exhibiting growth inhibition.

As noted by the Examiner, Chari fails to teach conjugates comprising anti-ErbB2 antibodies. The Examiner also notes that Hudziak fails to teach "that the patient has not responded or responded poorly to an unconjugated anti-ErbB2 antibody" (page 5, lines 6-8 of the present Office Action). Applicants note that Chari also fails to discuss tumors that fail to respond, or respond poorly, to antiErbB2 antibodies. Applicants respectfully submit that Claims 1, 2, 4, 5, 8-12, 20-33, and 38-41 are not obvious under 35 U.S.C. § 103(a) over the cited references.

Obviousness under 35 U.S.C. §103(a) requires several elements, and may not be directed by hindsight based on the disclosure under examination. Thus, the Federal Circuit has stated that:

> "In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure." In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Cited References Fail to Provide any Suggestion or Motivation to Combine

Applicants respectfully submit that there is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Hudziak and Lewis each fail to disclose and fail to suggest maytansinoid compounds. Thus, there is no link between these references apart from the present disclosure. Although the Examiner suggests that Lewis "teaches that some tumor cells that overexpress ErbB2 fail to respond to murine antibody 4D5" (page 5, lines 9-10 of the present Office Action), Applicants note that Lewis nowhere suggests methods for treating such tumors, and in particular, Lewis nowhere suggests treating such tumors with maytansinoids conjugated to those particular antibodies which Lewis showed did not inhibit the growth of such cells.

In fact, Lewis teaches away from the methods of the present invention. Lewis states that "The sensitivity of breast tumor cell lines to antibody-mediated growth inhibition correlates well with their level of $p185^{HER2}$ overexpression." (page 261, column 2, lines 27-30). Lewis thus teaches that cells that overexpress $p185^{HER2}$ can be treated with anti-ErbB2 antibodies alone. Lewis does not explain the discrepancy between their main conclusion (that antibody-sensitivity increases with increasing $p185^{HER2}$ overexpression) and their observation that some cells fail to respond to anti-ErbB2

antibodies. Lewis further fails to provide any hypothesis or suggestion to explain the existence of such non-responding cells. Moreover, Lewis also fails to suggest a possible treatment for such non-responding cells, and provides no basis for suggesting a possible treatment.

Moreover, Chari and Hudziak each also fail to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Accordingly, the cited references either teach away from, or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention.

The cited references fail to provide motivation to be so combined and fail to provide such a suggestion. Thus, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

As stated by the Federal Circuit: "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one or ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. ... Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999).

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 5, lines 14-17 of the Office Action, emphasis added). However, none of the cited references discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the cited references provide any motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population.

Applicants respectfully note that the question of whether or not it would have been surprising that such a population of patient exists is not that the proper standard for presenting a case for obviousness. Since none of the references suggests or motivates combination with other of the references to provide the claimed methods using anti-ErbB2 antibodies conjugated to maytansinoids, the Examiner's suggestion that it would not have been surprising if a population existed that did not respond to treatments that differ from the claimed treatment methods does not support a *prima facie* case of obviousness. The Federal Circuit has stated that "obvious to try is not the standard" *Ecolochem, Inc. v. Southern California Edison Co.,* 227 F.3d 1361, 56 USPQ2d 1065 (Fed Cir. 2000) and that "we have consistently held that 'obvious to try' is not to be equated with obviousness under 35 USC 103." *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

For this reason as well, Applicants respectfully submit that Chari, in view of Hudziak and in view of Lewis fail to make Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 obvious.

As noted above, the Examiner stated that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 5, line 14-17 of the Office Action, emphasis added). The basis for the underlined portion of the Examiner's statement is unclear, since none of the

references discuss an anti-ErbB2 antibody that was conjugated to a maytansinoid. It appears that the only suggestion for treatment of such tumors with an anti-ErbB2 antibody conjugated to a maytansinoid is derived from the present specification. As discussed above, hindsight is improper and may not be used to support a case for obviousness.

The Examiner also suggests that "the prior art recognized that an anti-ErbB2 antibody could be used for the purpose of delivering a cytotoxic moiety to a tumor, especially to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2." (page 6, lines 10-12 of the present Office Action.) However, no cited reference discusses or suggests using an anti-ErbB2 antibody to deliver a cytotoxic moiety to a tumor; thus the basis for the statement above is obscure. In addition, there is no teaching or suggestion in the cited references that an anti-ErbB2 antibody could be used to deliver a cytoxic moiety especially to tumors that do not respond to the ErbB2 antibody alone. This statement as well is not believed to be supported by the cited references. Thus, for these reasons as well, Applicants respectfully submit that the prior art does not suggest the present methods nor suggest that the cited references be combined to provide the claimed methods.

Cited References Fail to Provide a Reasonable Expectation of Success

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. In fact, Applicants respectfully submit that Lewis teaches away from the claimed methods by stating that, although for most cells "The sensitivity of breast tumor cell lines to antibody-mediated growth inhibition correlates well with their level of $p185^{HER2}$ overexpression." (page 261, column 2, lines 27-30) Lewis notes that some cells do not respond in this way. One of ordinary skill in the art would thus expect that, for those cells that do not respond, or respond poorly, to anti-ErbB2 antibodies (*i.e.,* for which the antibody treatment fails), other treatments based on such antibodies would also fail. Thus, being taught by Lewis that such antibody treatments would likely fail, and Chari and Hudziak also failing to provide reason to expect success in treating the target cell

population, the combination of the cited references fails to provide a reasonable expectation of success.

Accordingly, since 1) the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; and for other reasons discussed above, Applicants respectfully submit that Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 are not made obvious by the cited references.

Moreover, the present specification reports unexpected results. As discussed above, Lewis teaches that most cells that overexpress ErbB2 are susceptible to treatment by anti-ErbB2 antibodies, and that there are also some cells which do not respond to such antibodies. Surprisingly, the present inventors discovered methods for treating such non-responding, or poorly responding, cells using modified ant-ErbB2 antibodies – the same antibodies that were shown in the art not to affect such cells. Such unexpected results further illustrate that Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 are not obvious over the cited references.

The Rejections to Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 Under 35 U.S.C. §103(a)

Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Carter and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above. Carter is presented as providing humanized 4D5 antibodies, and in addition is said by the Examiner to teach each of huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8. Applicants respectfully submit that Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 are not obvious under 35 U.S.C. §103(a) over the cited references.

As discussed above regarding the rejections of Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 over Chari, Hudziak and Lewis, there is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Chari and Lewis are also cited in the present rejections of Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48. Carter is cited in place of Hudziak. However, like Hudziak and Lewis, Carter also lacks disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Carter also fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Carter). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention.

The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 7, lines 17-19 of the Office Action, emphasis added). The Examiner notes that Carter contemplated the use of immunotoxins in methods of treatment (page 7, lines 19-20 of the present Office Action) and suggests that since Carter discusses ErbB2 and since Lewis noted some ErbB2 overexpressing cells failed to respond to anti-ErbB2 antibodies, "one would have been motivated to use the antibodies of Carter to make the maytansinoid conjugates" (page 8, lines 1-5 of the present Office Action).

However, Carter nowhere contemplates treatments with maytansinoid-antiErbB2 antibody conjugates, and nowhere contemplates treatments of tumors that overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis does not suggest a treatment for such cells, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

As discussed above, the question of whether or not it would have been surprising that such a population of patient exists is not that the proper standard for presenting a case for obviousness. Applicants again respectfully note that the Federal Circuit has stated that "we have consistently held that 'obvious to try' is not to be

equated with obviousness under 35 U.S.C. §103." *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and Carter fail to discuss or to suggest the present methods and fail to suggest combining with other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; since 5), the present invention provides unexpected results; and for other reasons discussed above, applicants respectfully submit that Chari, in view of Carter and in view of Lewis fail to make Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 obvious.

The Rejections to Claims 1, 2, 4-6, 8-12, 14, 20-33, and 38-41 Under 35 U.S.C. §103(a)

Claims 1, 2, 4-6, 8-12, 14, 20-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Bacus et al. (U.S. Patent No.5,514,554, hereafter "Bacus") and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above, the Examiner stating that "Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody" (page 8, lines 11-12). Bacus is presented as providing anti-ErbB2 antibodies that are growth inhibitory, induce cell death, and that induce apoptosis, and that such antibodies may be conjugated to cytotoxic moieties. Applicants respectfully

submit that Claims 1, 2, 4-6, 8-12, 14, 20-33, and 38-41 are not obvious under 35 U.S.C. §103(a) over the cited references.

As discussed above regarding other combinations of references, there is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Like Lewis, Bacus also lacks disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Bacus also fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Bacus). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention.

The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 8, lines 19-21 of the Office Action, emphasis added). The Examiner notes that Bacus contemplated the use of immunotoxins in methods of treatment (page 9, lines 1-2 of the present Office Action) and suggests that since Bacus discusses immunotoxic conjugates and since Lewis noted some ErbB2 overexpressing cells failed to respond to anti-ErbB2 antibodies, "one would have been motivated to use the antibodies of Bacus to make the maytansinoid conjugates" (page 9, lines 4-7 of the present Office Action).

However, Bacus, which does not mention maytansinoid compounds, nowhere contemplates treatments with maytansinoid-antiErbB2 antibody conjugates, and provides no suggestion of such treatments. Bacus also fails to discuss or even suggest treatments of tumors that overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis fails to suggest a treatment for such cells, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

As discussed above, the question of whether or not it would have been surprising that such a population of patient exists is not that the proper standard for presenting a case for obviousness. Applicants again respectfully note that the Federal

Circuit has stated that "we have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. §103." *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and Bacus fail to discuss, or suggest, the present methods or to suggest combining with other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; since 5) the present invention provides unexpected results; and for other reasons discussed above, applicants respectfully submit that Chari, in view of Bacus and in view of Lewis fail to make Claims 1, 2, 4-6, 8-12, 14, 20-33 and 38-41 obvious.

The Rejections to Claims 1, 2, 8-14, and 20-33 Under 35 U.S.C. §103(a)

Claims 1, 2, 8-14, and 20-33 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Huston and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above, the Examiner stating that "Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments) and neither Chari nor Lewis teach methods for treatment of metastatic breast cancer." (page 9, lines 13-15). Huston is presented as providing single-chain Fv that bind to ErbB2, and methods of treating cancer comprising linking the Fv to an agent that can limit tumor proliferation, and methods for treating metastatic breast cancer (page 9, lines 17-21). Applicants

respectfully submit that Claims 1, 2, 8-14, and 20-33 are not obvious under 35 U.S.C. § 103(a) over Chari, Lewis and Huston.

Lewis and Huston each lack disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

Huston fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Huston). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention. The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would

respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 10, lines 3-6 of the Office Action, emphasis added). The Examiner notes that Huston contemplated the use of single-chain Fv linked to a therapeutic agent, (page 10, lines 6-7 of the present Office Action) and suggests that since Huston discusses such Fv conjugates and since Lewis noted some ErbB2 overexpressing cells failed to respond to anti-ErbB2 antibodies, "one would have been motivated to use the antibodies of Huston to make the maytansinoid conjugates" (page 10, lines 10-13 of the present Office Action).

However, Huston, which does not mention maytansinoid compounds, nowhere contemplates treatments with maytansinoid-antiErbB2 antibody conjugates, and provides no suggestion of such treatments. Huston also fails to discuss or even suggest treatments of tumors that overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis fails to suggest a treatment for such cells, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

As discussed above, Applicants note that the question of whether or not it would have been surprising that such a population of patient exists is not that the proper standard for presenting a case for obviousness, "obvious to try" not being equated with obviousness under 35 U.S.C. §103.

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and Huston fail to discuss, or suggest, the present methods or to suggest combining with

other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1) the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4) the cited references provide no reasonable expectation of success were the references to be so combined; since 5), the present invention provides unexpected results; and for other reasons discussed above, applicants respectfully submit that Chari, in view of Huston and in view of Lewis fail to make Claims 1, 2, 8-14, 20-33 obvious.

The Rejections to Claims 1, 2, 8-12, 22-33, and 38-41 Under 35 U.S.C. §103(a)

Claims 1, 2, 8-12, 22-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of King and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above, the Examiner stating that "Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments)." (page 10, lines 19-120). King is presented as providing methods for treating cancer that express high levels of ErbB2, using antibodies to ErbB2 linked to agents that are toxic to cells (page 11, lines 1-4). Applicants respectfully submit that Claims 1, 2, 8-12, 22-33 and 38-41 are not obvious under 35 U.S.C. §103(a) over Chari, Lewis and King.

Lewis and King each lack disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

King fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and King). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention. The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 11, lines 7-10 of the Office Action, emphasis added). The Examiner notes that King contemplated the use of an antibody linked to one or more agents that will cause injury to cells (page 11, lines 10-12 of the present Office Action) and suggests that since King discusses such antibodies linked to cell-toxic agents, and since Lewis noted some ErbB2 overexpressing cells failed to respond to anti-ErbB2 antibodies, "one would have been motivated to use the antibodies of King to make the maytansinoid conjugates" (page 11, lines 15-16) of the present Office Action).

However, King, which does not mention maytansinoid compounds, nowhere contemplates treatments with maytansinoid-antiErbB2 antibody conjugates, and provides no suggestion of such treatments. King does not discuss or even suggest treatments of tumors that overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis fails to suggest a treatment for such cells, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

As discussed above, applicants note that the question of whether or not it would have been surprising that such a population of patient exists is not that the proper standard for presenting a case for obviousness, "obvious to try" not being equated with obviousness under 35 U.S.C. §103.

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and King fail to discuss, or suggest, the present methods or to suggest combining with other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable

expectation of success were the references to be so combined; since 5), the present invention provides unexpected results; and for other reasons discussed above, applicants respectfully submit that Chari, in view of King and in view of Lewis fail to make Claims 1, 2, 8-12, 22-33, and 38-41 obvious.

The Rejections to Claims 1, 33, 44 and 45 Under 35 U.S.C. §103(a)

Claims 1, 34, 44 and 45 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in combination with Hudziak, Bacus, Huston, or King in view of Lewis as applied to Claim 1 and further in view of Senger.

Chari, Hudziak, Huston, King and Lewis are presented by the Examiner as discussed above. The Examiner characterizes Claims 1, 34,44 and 45 as drawn to treatment methods comprising administration of a maytansinoid conjugated to an antibody that binds ErbB2, and a second antibody that may be conjugated to any cytotoxic agent (page 12, lines 3-6). The Examiner states that Chari with Hudziak or Bacus or Huston or King fail to teach methods using combinations of at least two antibodies. Senger is presented to discuss treatment of tumors using at least two antibodies that bind to vascular permeability factor (VPF) and which may be conjugated to a toxin (page 12, lines 11-14).

However, except for Chari, all the cited references lack disclosure of maytansinoids, or of antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari and Senger lack any disclosure or suggestion of anti-ErbB2 antibodies. No relation between VPF and ErbB2 or between VPF antibodies and maytansinoids is suggested. Although the Examiner presents Senger as providing an example of a treatment strategy where an antigen is targeted with two different antibodies, where each antibody is conjugated with a toxin, there is no link apparent, and the Examiner provides no explanation for a link, between VPF and tumors which overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

The cited references also fail to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, Lewis actually teaches away from such treatments. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody.

The Examiner suggests that "because Senger provides an example of a treatment strategy where an antigen is targeted with two different antibodies, where each are conjugated to a toxin" (page 12, line 21 to page 13, lines 1-2), it would have been obvious to combine Chari with either of Bacus, Huston or King in view of Lewis. However, none of these references suggests or motivates such a combination, the references fail to teach a relationship between anti-VPF antibodies, treatments with such antibodies, and the present methods, and none of the cited references suggests or motivates methods of treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

Failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness. Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. Thus, applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 3), the cited references provide no reasonable expectation of success were the references to be so combined; since 4), the present invention provides unexpected results; and for other reasons discussed above, Applicants respectfully submit that the rejections of Claims 1, 34, 44 and 45 under 35 U.S.C. §103(a) are overcome.

The Rejections to Claims 1, 34-37, 42 and 43 Under 35 U.S.C. §103(a)

Claims 1, 34-37, 42 and 43 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in combination with Hudziak, Bacus, Huston, or King in view of Lewis as applied to claim 1 and further in view of Sliwkowski et al. (J. Biol. Chem. 269:14661-14665, 1994; hereafter "Sliwkowski") or Carter.

Chari, Hudziak, Bacus, Huston, King and Lewis have been discussed above. Sliwkowski is presented as discussing an anti-ErbB2 antibody, 2C4, that "may be used to inhibit the binding of heregulin (a growth factor) to ErbB3" and Carter is presented as discussing that "huMab4D5-8 acts to recruit immune effector cells to a tumor" (page 13, lines 17-20). The Examiner suggests that it would be obvious to rely on these references for the use of a second antibody to block the effects of a growth factor or to recruit immune effector cells to a tumor, citing *in re Kerkhoven* to suggest that the combination of two elements known to be useful for one purpose, to provide a third composition for that purpose.

The Examiner states that "In the instant case the first therapeutic composition is the anti-ErbB3-maytansinoid conjugate" (page 14, lines 9-10 of the Office Action). However, none of the references, including neither Sliwkowski nor Carter, discuss treatment of a tumor in a mammal where that tumor overexpresses ErbB2 and that tumor also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Such treatments are an important purpose of the present invention, and the purpose of the present claims. The cited references thus do not discuss a purpose of

the claimed invention. For at least this reason, it is not clear how *in re Kerkhoven* applies to the present rejections.

In addition, as discussed above, such a therapeutic composition is not obvious over any combination of the cited references; the claimed therapeutic methods are not suggested not motivated by the cited references. However, as acknowledged by the Examiner, an *in re Kerkhoven* analysis requires that "each of the two compositions is taught by the prior art to be useful for the same purpose" (page 14, lines 7-8 of the Office Action). As discussed above, the conjugates of the claimed methods are not taught by the prior art; nor are they suggested by the prior art; nor does any reference or combination of references suggest the purpose of the methods of the present claims. Thus, there is no basis in the art for the sort of *in re Kerkhoven* analysis suggested by the Examiner, nor would such an analysis provide the methods of the present claims, lacking both the compositions and the purpose for which those compositions are applied (to treat tumors in an mammal that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody).

Moreover, the present disclosure provides unexpected results. The target tumors of the present invention are those that do not respond, or respond poorly to anti-ErbB2 antibodies, so that treatments based on these antibodies would not be expected to be work. Surprisingly, the present inventors have shown that anti-ErbB2 antibodies conjugated with maytansinoids are useful in treating tumor cells that do not respond, or respond poorly to anti-ErbB2 antibodies. As discussed in *in re Kerkhoven*, it appears that one may refute an allegation of obviousness where inventors show superiority over the cited references (see, *e.g.,* page 1973, column 1, lines 3-10, discussing Kerkhoven's failure to do so). Thus, for this reason as well, Applicants submit that Claims 1, 34-37, 42 and 43 are not obvious over the cited references.

The cited references thus fail to suggest or motivate a combination to provide the claimed methods, and provide no reasonable expectation of success for such a combination, since no reference discusses any method of treating the target tumor population. Moreover, as discussed above, the present specification discloses

unexpected results. Accordingly, applicants submit that the rejections of Claims 1, 34-37, 42 and 43 under 35 U.S.C. § 103(a) are overcome.

The Rejections to Claims 1, 4-6, 8-19, 22-25, 27 and 32 Under 35 U.S.C. §103(a)

Claims 1, 4-6, 8-19, 22-25, 27 and 32 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Iwassa in combination with Carter, Hudziak, Bacus, Huston, or King in view of Lewis.

Carter, Hudziak, Bacus, Huston, King and Lewis are presented by the Examiner as discussed above. Iwassa is presented by the Examiner as providing an immunocomplex that comprises a bispecific antibody that binds to a tumor antigen and to a maytansinoid. The Examiner also states that Iwassa "fails to teach that the immunocomplex binds to the ErbB2 tumor antigen" (page 15, lines 5-6 of the present Office Action). Applicants note that Iwassa also fails to suggest targeting tumors that overexpress the ErbB2 tumor antigen and also fail to respond, or only respond poorly, to anti-ErbB2 antibodies. The Examiner cites Carter, Hudziak, Bacus, Huston and King as discussing that the ErbB2 tumor antigen is useful for targeting, and Lewis as discussing that some tumor cells that overexpress ErbB2 fail to respond to anti-ErbB2 antibodies. However, the cited references nowhere suggest targeting a tumor for treatment with anti-ErbB2 antibodies conjugated with maytansinoids where that tumor is known not to respond to such anti-ErbB2 antibodies.

Thus, there being no suggestion to combine the cited references in those references themselves, such a suggestion must come from the present disclosure, and so be based on impermissible hindsight, or arise out of a belief that it might have been obvious to try such a combination. However, as discussed above, "obvious to try" may not be equated with obviousness under 35 U.S.C. §103.

As discussed above the cited references provide no suggestion or motivation to provide a treatment for such target tumors and provide no suggestion or motivation for treating such target tumors with anti-ErbB2 antibodies conjugated with maytansinoids. Iwassa does not make up for this lack of suggestion or motivation, not discussing ErbB2, nor anti-ErbB2 antibodies, and nowhere discussing or suggesting targeting

tumors which overexpress ErbB2 yet do not respond to anti-erbB2 antibodies. Failing this, Iwassa and the other cited references fails to provide any reasonable expectation of success for such a combination.

Moreover, as discussed above, the present results are surprising and unexpected.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 3), the cited references provide no reasonable expectation of success were the references to be so combined; since 4), the present invention provides unexpected results; and for other reasons discussed above, applicants respectfully submit that the rejections of Claims 1, 4-6, 8-19, 22-25, 27 and 32 under 35 U.S.C. §103(a) are overcome.

CONCLUSION

Applicants respectfully submit that Claims 1, 2, 4-6, and 8-48 stand in allowable form, and respectfully request their reconsideration and allowance. Early notification of the allowance of all claims is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0073 A2**.

Respectfully submitted,

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